Topic 28 – Hypertension, remodeling, arterial stiffness – C

April 02nd, Thursday 2015

0214

Mineralocorticoid Receptor (MR) activation induces the expression of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in dendritic cells in vitro and during the aldosterone-dependent hypertension

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Introduction: Inadequate activation of the Mineralocorticoid Receptor (MR) promotes hypertension, inflammation and fibrosis. Neutrophil Gelatinase-Associated Lipocalin (NGAL), a pro-inflammatory/fibrotic glycoprotein, is a target of MR-genomic upregulation in cardiovascular cells, and is increased in immune cells during inflammation. Recently, we have demonstrated that NGAL is crucial for hypertensive effects of aldosterone-salt (NAS) challenge in mice. The specific cell types that modulate the NGAL production during Aldosterone (Aldo)-dependent hypertension are unknown. The aim was to characterize the NGAL expression in mouse immune cells, and to study the effect of MR activation on the NGAL and pro-inflammatory cytokines expression in dendritic cells (DCs).

Methods: Male C57Bl6 mice were treated in groups Sham and NAS (200µg/kg/d, 28 days). Peripheral blood mononuclear cells (PBMC) were isolated, and $CD4^+$, $CD8^+$ T cells, B cells, DCs and Macrophages (Mø) were sorted from spleen. DCs and Mø were cultured from WT and NGAL-KO mice and treated with Aldo (100nM) or vehicle for 24hrs. NGAL and cytokines mRNAs abundance was measured by qRT-PCR.

Results: NAS mice presented high systolic blood pressure (123 mmHg *vs.* Sham 101±6 mmHg, $p<0.05$), cardiac and renal hypertrophy. Additionally, NAS treatment induced a selective increase in the recruitment of activated-$CD8^+$ cells, B cells and granulocytes in lymph nodes. NGAL abundance was higher in PBMC, DCs and Mø, which were further increased in NAS mice (<3-fold vs. Sham, $p<0.05$ mRNA). *In vitro* MR activation by Aldo in DCs, but not in Mø, induced an upregulation of NGAL and of cytokines involved in the adaptive immune response: TGF-β1 and IL-23p19 ($n=4$, $p<0.05$). Interestingly, the NGAL absence in DCs prevented this overexpression.

Conclusion: The MR activation and their subsequent NGAL induction in DCs could play a pivotal role in the inflammation observed during the Aldo-dependent hypertension.

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Genetics of hypertension

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Background: High blood pressure is one of the most important modifiable risk factors for cardiovascular disease; the prevalence of hypertension in Moroccan population is 33.6%

Hypertension is a complex, multifactorial and may be triggered by the genetic and environmental factors.
The heritable component of blood pressure has been documented in familial and twin studies suggesting that 30%-50% of the variance of blood pressure readings are attributable to genetic heritability and also to environmental factors.

Methods: A total of 101 patients with hypertension were included and stratified by cardiovascular risk. We studied the genetic variability of two genes: the MTHFR gene (C677T) involved in vascular factors and the ACE gene (I / D) which is part of the renin-angiotensin-aldosterone system.

Results: 33.66% of our population (gender confused) had a higher risk, 40.59% had a medium risk, while 25.75% had a low risk. Concerning the genetic study, we found an allele frequency (D) of ACE gene of 84.2% without susceptibility to hypertension whatever the genotype ($p = 0.3$ and 0.1 genotypes ID and DD, respectively) and a gene frequency (T) of 53.5% of the MTHFR gene with a statistically significant surisque of homozygous mutant TT ($p = 0.042$).

Conclusion: The D allele of the ACE gene is not correlated with hypertension predisposition while the T allele of the MTHFR gene is associated with hypertension in its homozygous form.

0382

Exome sequencing in seven families and gene-based association studies indicate genetic heterogeneity and suggest possible candidates for fibromuscular dysplasia

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Fibromuscular dysplasia (FMD) is a nonatherosclerotic vascular disease leading to stenosis, aneurysm and dissection, mainly of renal arteries and carotids. FMD occurs predominantly in females with ~4/1000 prevalence and cause hypertension, renal ischemia or stroke. The pathogenesis of FMD is unknown and a genetic origin is suspected given its demonstrated familial aggregation. We performed whole exome sequencing (WES) in 16 cases (seven families). Coding variants in 3,971 genes were prioritized on frequency (minor allele frequency <0.01) and in silico predicted functionality. No gene harbors variants that are shared among all affected members of at least three families. Variants from 16 genes of vascular and connective tissue diseases are excluded as causative in these families. Genes with at least four variants in the 16 patients and vascular genes were followed-up using genotypes from 249 unrelated cases and 689 controls. Gene-based association analyses using SKAT-O shows nominal significant association with multifocal FMD (N=164) for myosin light chain kinase (MYLK, P=0.01) previously involved in thoracic aortic aneurysm, obscurin (OBSCN), a sarcomeric protein (P=0.003), dynein cytoplasmic heavy chain 1 (DYNC2H1, P=0.02) and RNF213 previously associated with Moyamoya disease (P=0.01). Our study indicates genetic heterogeneity and the unlikely existence of a major gene for FMD and excludes the role of several vascular genes in familial FMD. We also suggest four possible candidate genes for multifocal FMD, though these findings need further genetic and functional confirmation. More powerful WES and association studies (e.g. GWAS) will better decipher the genetic basis of FMD.

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Molecular mechanisms involved in the vascular protection induced by estrogen receptor alpha during hypertension in the mouse

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Women, before menopause, are less affected than men by hypertension and atherosclerosis, the main causes of cardiovascular diseases. Estrogens have been shown to protect the vascular endothelium through their nuclear receptors, mainly via the estrogen receptor alpha (ERα). However, recent studies have shown that a fraction of ERα is located at the cell membrane where it initiates a Membrane Initiated Steroid Signaling (MISS). Both membrane and nuclear pathways of ERα play a protective role in endothelial cells but their respective role in hypertension is unknown. To investigate the protective effects of ERα in hypertension, we used (i) mice lacking ERα (ERα-/-), (ii) mice with a point mutation of the palmitoylation site of ERα (C451A-ERα)